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Patent
Attorney Docket No. 82508
Customer No. 23685

TRANSMITTAL LETTER

Inventors: Reimo Tetzner et al.
Serial No: 10/568,300
Filed: February 15, 2006
Group Art Unit: 1645
For: METHOD FOR THE DETECTION OF CYTOSINE METHYLATIONS IN DNA

Confirmation No. 7918
Examiner: Unknown
Batch No:
Notice of Allowance:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Transmitted herewith for the above-identified patent application are the following:

An English Translation of the International Preliminary Report on Patentability
A return postcard

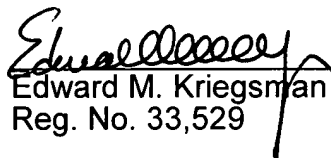
The item(s) checked below are appropriate:

1. ☐ Applicant(s) hereby petition(s) for a () month extension of time to respond to an dated

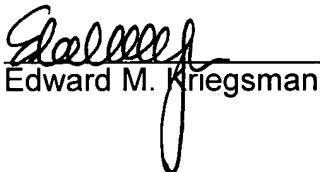
2. ☒ Please charge any fees or costs not accounted for to Deposit Account No. 11-1755.

Date: *November 7, 2006*

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on *November 7, 2006*


Edward M. Kriegsmann

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference P1199PC00	FOR FURTHER ACTION		See item 4 below
International application No. PCT/DE2004/001837	International filing date (<i>day/month/year</i>) 13 August 2004 (13.08.2004)	Priority date (<i>day/month/year</i>) 15 August 2003 (15.08.2003)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant EPIGENOMICS AG			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | |
|--|---|
| <input checked="" type="checkbox"/> Box No. I | Basis of the report |
| <input checked="" type="checkbox"/> Box No. II | Priority |
| <input type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> Box No. VI | Certain documents cited |
| <input type="checkbox"/> Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 03 July 2006 (03.07.2006)
	Authorized officer Ellen Moyse e-mail: pt05@wipo.int

PATENT COOPERATION TREATY

Translation

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:

Date of mailing
(day/month/year)

Applicant's or agent's file reference

P1199PC00

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/DE2004/001837

International filing date (day/month/year)

13.08.2004

Priority date (day/month/year)

15.08.2003

International Patent Classification (IPC) or both national classification and IPC

Applicant

EPIGENOMICS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP

Authorized officer

Facsimile No.

Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/DE2004/001837

Box No. I

Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language
_____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/DE2004/001837

Box No. II

Priority

1. ☐ The following document has not yet been furnished:
 - ☐ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the priority document was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/DE2004/001837

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-31</u>	YES
	Claims	_____	NO
Inventive step (IS)	Claims	_____	YES
	Claims	<u>1-31</u>	NO
Industrial applicability (IA)	Claims	<u>1-31</u>	YES
	Claims	_____	NO

2. Citations and explanations:

Reference is made to the following documents:

- D1: US 6,331,393 (18 December 2003)
D2: US 6,326,145 (4 December 2001)
D3: WO 99/66071 (23 December 1999)
D4: Whitcombe D et al. (1999), Nature Biotechnology, vol. 17, pages 804-807
D5: Thelwell N et al. (2000), Nucl. Acids Res., vol. 28, no. 19, pages 3752-3761
D6: Walker NJ (2001), J. Biochem. Molecul. Toxicol., vol. 15, no. 3, pages 121-127
D7: Pham P et al. (July 2003), Nature, vol. 424, pages 103-107
D8: Bransteitter R et al. (April 2003), PNAS, vol. 100, no. 7, pages 4102-4107
D9: Cottrell S et al. (March 2003), Ann. N.Y. Acad. Sci., vol. 983, pages 120-130

NOVELTY:

1. None of the documents to be taken into account discloses the subject matter of **claims 1-31**. The claims thus appear to meet the requirements of PCT Article 33(2).

INVENTIVE STEP

- 1.a **Claim 1** of the present application relates to a method for the detection of cytosine methylations in DNA by means of bisulphite treatment and subsequent quantitative real time PCR

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/DE2004/001837

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

using scorpion primers.

D1 and D2 respectively disclose methods for the detection of cytosine methylations in DNA by means of bisulphite treatment and subsequent quantitative fluorescence detection-based real time PCR using e.g. "TaqMan®", "Lightcycler®" or "Sunrise®" technologies (see, e.g. D1, abstract; column 1, lines 5-11; column 5, line 15-column 6, line 56; column 9, lines 17-37; column 13, line 26-column 16, line 52; claims 1-26; D2, abstract; paragraphs [0038]-[0041]; claims 1-25).

The method according to claim 1 thus differs from D1 and D2 in that it requires the use of scorpion primers. The problem addressed is therefore providing an alternative method which is characterized, e.g., by a rapid signal generation/suitability for rapid cycles, high specificity and/or reduced background detection.

The method according to claim 1 solves this problem. However, this solution is not inventive within the meaning of PCT Article 33(3) for the following reasons:

D3-D6 each disclose the use of scorpion primers in quantitative fluorescence detection-based real time PCR methods (see e.g. D3 abstract; page 3, line 15 - page 12, line 3; claims 1-24; D4, abstract; page 804, left-hand column; D5, abstract; page 3760; D6, figure 2). D3-D5 in this context explicitly teach that the use of scorpion primers in real time assays necessitates rapid signal generation (D3, page 11, lines 18-22; D4, page 804, left-hand column, last paragraph; page 806, last paragraph; D5, abstract; page 3757, left-hand column; page 3760, bridge between columns), high specificity and/or reduced background detection (D3, page 11, lines 18-22; D4, page 804, left-hand column, last paragraph; page 806, right-hand column, last paragraph; D5, page 3760, right-hand column).

A person skilled in the art addressing the above-formulated

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/DE2004/001837

Box No. V	Reasoned statement under Rule 43bis.1(a)(i).with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
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problem would, in the light of this teaching, combine **D1 or D2 with one of the documents D3-D6** and already by this means, i.e. in the absence of an inventive step, arrive at the method according to **claim 1**.

1.b Similar objections under PCT Article 33(3) may be formulated for the **use claim 30**.

2. The uses of cytosine methylation detection methods cited in **claim 29** were, at the priority date of the present application, routine applications (see for instance D1, columns 3-5; D2, paragraphs [0002]-[0015]). Therefore, this claim is not inventive under PCT Article 33(3).

3. The further features of dependent **claims 2-28** likewise do not appear suitable to support the inventive step required pursuant to PCT Article 33(3), since, at the priority date of the present application, they were standard variations, and thus belonged to the common specialist knowledge of a person of average skill in the art (see for instance D1-D9).

4. **D3** discloses kits containing at least one scorpion primer (D3, claim 24). Since scorpion primers are intended for use in PCR reactions (see D3-D6), providing a polymerase and also the reagents required for a polymerase chain reaction does not support an inventive step under PCT Article 33(3).